HHS Public Access

Author manuscript

Contraception. Author manuscript; available in PMC 2024 April 04.

Published in final edited form as:

Contraception. 2016 December ; 94(6): 641–649. doi:10.1016/j.contraception.2016.06.012.

Safety of hormonal contraception and intrauterine devices among women with depressive and bipolar disorders: a systematic review☆

H. Pamela Pagano[a,*], **Lauren B. Zapata**[a], **Erin N. Berry-Bibee**[a], **Kavita Nanda**[b], **Kathryn M. Curtis**[a]

[a]Division of Reproductive Health, US Centers for Disease Control and Prevention, 4770 Buford Hwy, MS F-74, Atlanta, GA 30341, USA

[b]FHI360, Durham, NC, USA

Abstract

Background: Women with depressive or bipolar disorders are at an increased risk for unintended pregnancy.

Objective: To examine the safety of hormonal contraception among women with depressive and bipolar disorders.

Methods: We searched for articles published through January 2016 on the safety of using any hormonal contraceptive method among women with depressive or bipolar disorders, including those who had been diagnosed clinically or scored above threshold levels on a validated screening instrument. Outcomes included changes in symptoms, hospitalization, suicide and modifications in medication regimens such as increase or decrease in dosage or changes in type of drug.

Results: Of 2376 articles, 6 met the inclusion criteria. Of three studies that examined women clinically diagnosed with depressive or bipolar disorder, one found that oral contraceptives (OCs) did not significantly change mood across the menstrual cycle among women with bipolar disorder, whereas mood did significantly change across the menstrual cycle among women not using OCs; one found no significant differences in the frequency of psychiatric hospitalizations among women with bipolar disorder who used depot medroxyprogesterone acetate (DMPA), intrauterine devices (IUDs) or sterilization; and one found no increase in depression scale scores among women with depression using and not using OCs, for both those treated with fluoxetine and those receiving placebo. Of three studies that examined women who met a threshold for depression on a screening instrument, one found that adolescent girls using combined OCs (COCs) had significantly improved depression scores after 3 months compared with placebo, one found that OC users had similar odds of no longer being depressed at follow-up compared with nonusers, and one found that COC users were less frequently classified as depressed over 11 months than IUD users.

☆Disclaimer: The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the US Centers for Disease Control and Prevention.

*Corresponding author. fax: +1 770 488 6391. hpagano@cdc.gov (H.P. Pagano).

Conclusions: Limited evidence from six studies found that OC, levonorgestrel-releasing IUD and DMPA use among women with depressive or bipolar disorders was not associated with worse clinical course of disease compared with no hormonal method use.

Keywords

Depression; Bipolar disorder; Hormonal contraception; Intrauterine device; Systematic review

1. Introduction

Mental health disorders are debilitating illnesses that affect both men and women. The most common mental health disorders that affect mood are depression with a lifetime prevalence of 16.6% and bipolar disorder with a lifetime prevalence of 3.9% in the United States [1]. According to the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*, depression is a disorder that may make a person feel sad, empty or in an irritable mood, which may in turn affect the person's ability to function in normal activities [2]. The prevalence of depression in women of reproductive age has been reported to be about 14% [3], and it is almost twice as common in women as in men [4]. Bipolar disorder is characterized by depressive and manic or hypomanic episodes [5] in which patients may experience unusual and abnormal patterns in mood, energy, activity levels and sleep [5]. Bipolar disorder has an early age of onset [6], with the highest prevalence in the 18- to 29-year age group [1]. The prevalence of bipolar disorder in women is between 1% and 2%, with the mean age of onset at approximately 20 years [7].

Depressive and bipolar disorders have been associated with unintended pregnancy, risky sexual behaviors and lack of consistent and effective contraceptive use [8–11]. Moreover, depression symptoms during pregnancy may lead to adverse obstetric, fetal and neonatal outcomes [3,12,13]. Women with depressive or bipolar disorders may experience risks during pregnancy, such as teratogenic effects to the fetus from the medications for the disorder or worsening of symptoms during pregnancy [14]. An unintended pregnancy may also lead to or worsen depressive symptoms [15].

Little is known about the safety of contraceptive use among women with these disorders. Studies that have linked hormonal contraceptive use to mood changes and subsequent discontinuation of oral contraceptive (OC) use in healthy women have raised the possibility that these methods may worsen symptoms in women with diagnosed disorders [16–18]. Proposed biological theories for mood changes in normal women using hormonal contraceptives include estrogen-induced pyridoxine deficiency or estrogen or progestin interaction with the serotonergic system or noradrenergic systems [19]. Given the high prevalence of depressive and bipolar disorders among women of reproductive age and the public health importance of preventing unintended pregnancies, the objective of this review was to examine the safety of hormonal contraception among women with depressive and bipolar disorders.

2. Materials and methods

We conducted this systematic review according to the PRISMA guidelines [20], using the following key question: are women of reproductive age with depressive or bipolar disorders who use hormonal contraception at increased risk for adverse outcomes compared with women using nonhormonal methods or no method of contraception?

2.1. Literature search

We searched the PubMed database for peer-reviewed articles published in any language from database inception through January 2016 using the following search strategy:

> ((((mood disorders[MESH] OR depression[MESH] OR mood*[TIAB] OR depression[TIAB] OR depressive[TIAB] OR affective disorder*[TIAB] OR bipolar[TIAB]))))) AND ((“Contra-[Mesh] OR “Contraceptives, Oral”[Mesh] OR “Contraceptives, Oral, hormonal”[Mesh] OR “Contraceptives, Oral, Combined”[Pharmacological Action]) OR (contracept* AND (oral OR pill OR tablet)) OR ((combined hormonal) OR (combined oral) AND contracept*) OR (contracept* AND (ring OR patch)) OR “ortho evra” OR nuvaring OR (progestin* OR progestins [MeSH] OR Progesterone[MeSH] OR progesterone OR progestogen* OR progestagen* OR “Levonorgestrel” [Mesh] OR levonorgestrel OR “Norgestrel”[Mesh] OR norgestrel OR etonogestrel AND contracept*) OR dmpa OR “depot medroxyprogesterone” OR “depo provera” OR “net en” OR “norethisterone enanthate” OR “norethindrone enanthate” OR (contracept* AND (inject* OR implant)) OR ((levonorgestrel OR etonogestrel) AND implant) OR implanon OR nexplanon OR jadelle OR norplant OR uniplanar OR sinoimplant OR (levonorgestrel-releasing two-rod implant) OR “Intrauterine Devices”[Mesh] OR “Intrauterine Devices, Copper”[Mesh] OR “Intrauterine Devices, Medicated”[Mesh] OR ((intrauterine OR intra-uterine) AND (device OR system OR contracept*)) OR IUD OR iucd OR IUS OR mirena OR skylab OR paragard OR “Copper T380” OR CuT380 OR “Copper T380a” OR “Cu T380a”) NOT (“Animals”[Mesh] NOT “Humans”[Mesh])

We used similar search strategies to identify potential articles in the PsychInfo and Cochrane Library databases and hand-searched reference lists from articles identified by the search and key review articles.

2.2. Selection criteria

We included studies among women of reproductive age with either depressive disorder or bipolar disorder [2], which we defined as either (1) being diagnosed clinically with the disorder or (2) having scored above threshold levels on a validated mood disorder screening instrument.

We included studies examining the use of hormonal contraception, including combined hormonal contraceptives [combined OCs (COCs), patches and vaginal rings] and progestin-only contraceptives [progestin-only pills (POPs), injectables, implants and the levonorgestrel-releasing (LNG) intrauterine device (IUD)]. We noted the type of OC

examined if described in the study (i.e., COC or POP), otherwise indicated that the OC type was not specified. The comparison group included women using nonhormonal methods (including the copper IUD) or no method.

We considered several potential adverse outcomes including changes in depressive or bipolar disorder symptoms, hospitalization, suicide and modifications in medication regimen for treatment of the disorder such as increase or decrease in dosage or changes in type of drug.

We excluded studies that examined whether the use of hormonal contraception among healthy women increased their risk of our outcomes of interest, unless data were analyzed separately for subgroups of women diagnosed with or screening positive for a depressive or bipolar disorder. We also excluded studies that evaluated the use of hormonal contraception on premenstrual symptoms. We included randomized controlled trials (RCTs), cohort studies and case–control studies; all other study designs were excluded.

2.3. Study quality assessment and data synthesis

The evidence was summarized and systematically assessed using standard abstraction forms. The quality of each individual piece of evidence was assessed using the grading system developed by the United States Preventive Services Task Force [21]. We focused on several study factors when assessing quality, including study design, assessment of contraceptive use, timing of contraceptive use relative to outcome assessment, adjustment for potential confounders and participation and follow-up rates. We did not compute summary measures of association due to heterogeneity across the included studies related to study population, classification of exposure and outcomes reported.

3. Results

The search strategy identified 2376 articles, of which 6 [10,22–26] met our inclusion criteria (Tables 1 and 2). The majority of studies were excluded as they did not pertain to our key question. Others were excluded due to study design, inclusion of healthy women without reporting results separately for women with or screening positive for a depressive or bipolar disorder, or because they did not describe use of a screening instrument or the threshold level used to identify possible depressive or bipolar disorders.

Three of the studies examined women with a clinical diagnosis of bipolar disorder or depression [10,24,25], while the other three used validated instruments to screen for depression [22,23,26]. Most studies examined women aged 18 to 45 years [10,24–26], but two focused on young women [23] or adolescents [22]. Sample sizes ranged from 17 [24] to 9688 [23]. Four studies compared OC users with nonusers; one examined COCs [22], one examined OCs (most of which were COCs) [25] and two examined OCs (type not specified) [23,24]. One study compared COC users with IUD users (type not specified, but assumed to be nonhormonal) [26], and one study compared women using depot medroxyprogesterone acetate (DMPA), LNG-IUDs, Cu-IUDs and sterilization [10].

3.1. Studies of women clinically diagnosed with depressive or bipolar disorders

One prospective cohort study examined the effect of OCs (type not specified) on daily self-reported mood ratings for three menstrual cycles in 17 women aged 18–45 years with bipolar disorder [24]. All women were taking mood stabilizers for bipolar disorder and 71% were also taking antidepressants; the specific types, doses or duration of use for these medications were not specified. Mood was assessed using a 100-mm visual analog scale, with scores less than 40 considered depression, scores between 40 and 60 considered normal, and scores greater than 60 considered hypomania. Among OC users (n=6), mood did not significantly change over the menstrual cycle (mean of 50.1 in the first 7 days vs. 49.1 in the last 7 days, p=.510), whereas mood did significantly change across the menstrual cycle among women not using OCs (n=11) (mean of 38.2 in the first 7 days vs. 41.3 in the last 7 days, p=.015) (Table 1).

Another prospective cohort study examined the frequency of hospitalizations for bipolar disorder or depression over 12 months among 841 women aged 18–44 years diagnosed with bipolar disorder [10]. Study participants were identified through a nationwide health insurance database. Women were DMPA users (n=182), LNG-IUD users (n=139) or Cu-IUD users (n=113), or had undergone sterilization (n=407). No significant differences were observed among the four contraceptive groups in the number of hospitalizations for bipolar disorder (6.0%, 3.6%, 5.3% and 5.7% for DMPA, LNG-IUD, Cu-IUD and sterilization, respectively) or depression (2.2%, 0.7%, 0.9% and 3.2% for DMPA, LNG-IUD, Cu-IUD and sterilization, respectively) (p values not reported) (Table 1).

One prospective cohort analysis of data from 17 RCTs of fluoxetine safety and efficacy from a clinical trials database examined changes in depression scores among 866 women aged 18 to 45 years with a diagnosis of major depression [25]. The study included 120 OC users; OC types varied, but 83.5% were COCs. The study examined changes from baseline to endpoint in three separate scores based on the 17-item Hamilton Depression Scale (HAMD-17): (1) HAMD-17 total scores (50-point scale), (2) anxiety/somatization subscale scores (18-point scale) and (3) retardation subscale scores (14-point scale). Women had at least one post-baseline visit, but the authors did not report the range of follow-up times. Among women treated with fluoxetine, approximate baseline to endpoint reductions in all three scale scores were about the same for women using OCs (n=79) compared with women not using OCs (n=502), although statistical testing was not conducted for these comparisons: −9 vs. −8.75, respectively, for the total score; −2.5 vs. −2.5, respectively, for the anxiety/somatization subscale score; and −3.25 vs. −3, respectively, for the retardation subscale score. Among women receiving placebo, approximate baseline to endpoint reductions were roughly the same for women using OCs (n=41) compared with women not using OCs (n=215), although statistical testing was not conducted for these comparisons: −6 vs. −7, respectively, for the total score; −1.5 vs. −2, respectively, for the anxiety/somatization subscale score; and −2 vs. −2.25, respectively, for the retardation subscale score. Depression scale scores did not increase for any group of women (Table 1).

3.2. Studies of women classified as depressed based on depression scales

One RCT examining the efficacy of COCs for the treatment of dysmenorrhea among adolescent girls (*n*=76) also examined the effect of COCs vs. placebo on changes in depression scores [22]. Depression scores were assessed at baseline and at 3-month follow-up using the Center for Epidemiologic Studies Depression Scale (CESD; 60-point scale); adolescents were classified as depressed if they scored 27 or more. Among adolescents depressed at baseline (*n*=11), CESD scores significantly (p=.003) improved from baseline to endpoint (mean of 35.7 vs. 19.1, respectively), with similar improvements in the COC and placebo groups (data not reported) (Table 2).

One prospective cohort study examined the effect of current OC use (type not specified) on changes in classification of depression in women (*n*=9688) sampled from a national health insurance database and completed surveys in 1996 (Survey 1), 2000 (Survey 2) and 2003 (Survey 3) [23]. Women were classified as depressed if they scored 10 or greater on the CESD-10 (30-point scale). Among women depressed at Survey 2 (*n*=2488), women who started using OCs between Surveys 2 and 3 [adjusted odds ratio (AOR)=1.15, 95% confidence interval (CI)=0.75–1.76) and women who used OCs on both Surveys 2 and 3 (AOR=1.01, CI=0.73–1.41) had similar odds of no longer being depressed by Survey 3 than did women not using OCs at either time point, after adjustment for confounders (not described) (Table 2).

Another prospective cohort study examined changes in classification of depression over 11 months among women attending a family planning clinic [26]. Women taking COCs (*n*=218) were compared with women using IUDs (*n*=54); the type of IUDs was not specified but assumed to be nonhormonal due to the date of the study. Method continuation was low and varied by group (37% among COC users and 74% among IUD users). Also, 44% of COC users stopped or changed COCs and 19% were lost during follow-up; 13% of IUD users were lost during follow-up. Women were classified as depressed if they scored less than 9 on a modified Beck Depression Inventory (possible total score not reported). Among women depressed at baseline (*n*=75), significant (pb.5) differences between contraceptive groups (IUD users, continuing COC users, women who stopped or changed COCs) were observed at 5, 8 and 11 months, with lower proportions of continuing COC users classified as depressed (24%, 11% and 16%, respectively) than IUD users (58%, 42% and 40%, respectively) and women who stopped or changed COCs (72%, 56% and 59%, respectively) (Table 2).

4. Discussion

We identified six studies that examined hormonal contraceptive use among women with depressive or bipolar disorders, none of which found that hormonal contraceptives negatively influenced either condition. Four of these studies examined women with depression or women who scored above a threshold on a validated depression screening instrument, and all four found that COC or OC use was not associated with increased depressive symptoms compared with nonusers [22,23,25,26]. One study of women with bipolar disorder reported that OC users did not have significant mood changes across the menstrual cycle, but that those not taking OCs did have significant mood changes [24].

Another study found that the frequency of psychiatric hospitalizations for women with bipolar disorder did not significantly differ between women using DMPA, LNG-IUD, Cu-IUD or sterilization [10].

Health care providers may be concerned that medications used to treat mental health conditions may interact with their patient's contraceptive method. A recent systematic review concluded that although there is scant clinical or pharma-cokinetic data, many common psychotropic drugs used to treat anxiety and depressive disorders are unlikely to interact with hormonal contraceptive methods [27]. However, hormonal contraceptives may inhibit the metabolism of psychotropic drugs metabolized by the cytochrome P450 1A2 enzyme, resulting in potentially increased drug exposure and safety concerns for drugs with a narrow therapeutic window (e.g., tricyclic antidepressants) [27].

Providing contraception for women with postpartum depression or for women with depression during a recent pregnancy may also be of concern to providers. Postpartum depression includes major and minor depressive episodes that occur within the first 12 months after delivery, and it is estimated that as many as 19% of women have a depressive episode during the first 3 months postpartum [28]. Although we found no studies that specifically examined hormonal contraceptive use among women with postpartum depression, findings among non-postpartum women are likely relevant. Contraceptive use during the postpartum period can decrease the risk of rapid repeat pregnancy and its associated adverse effects in women with depressive or bipolar disorders.

Several limitations exist for this body of evidence. First, no standard definition or assessment of depressive and bipolar disorders or symptoms was used across studies. Of the four studies that used validated depression scales [22,23,25,26], each used a different scale and threshold level to classify participants as having the disorder or screening positive. Additionally, two studies determined thresholds from mean depression scores among study participants at baseline rather than recommended thresholds from published literature [22,26]. Two studies did not specify the type of OCs examined [23,24], and all five studies that examined OCs relied on self-report [22–26]. One study misclassified women using hormone therapy as OC users without stratifying findings [25]. Additionally, the timing of OC use relative to outcome measurement was not reported in two studies [23,25]. Poor method continuation rates were observed in two studies, among DMPA users in one [10] and among COC users in the other [26]. Four studies did not consider potential confounders or establish baseline comparability between study groups [10,24–26], and one did not report the specific confounders adjusted for during analyses [23]. Also, depression medication use was unknown in three studies [22,23,26]. Several studies had small sample sizes or few women classified as depressed at baseline [22,24,26], and findings from two studies may not be generalizability to women without health insurance [10,23]. Short follow-up or unknown follow-up time was a limitation in four studies [22,24–26]. Due to these limitations, the RCT was rated as having poor quality [22], three of the prospective cohort studies were rated as having poor quality [24–26], and two of the prospective cohort studies were rated as having fair quality [10,23].

In conclusion, evidence from one RCT [22] and five prospective cohort studies [10,23–26] suggests that COC or OC (type not specified), LNG-IUD and DMPA use among women with depressive or bipolar disorders was not associated with worse clinical course of disease compared with no hormonal method use (body of evidence grading Level I, poor to Level II-2, to poor). No evidence was identified for any other hormonal methods of contraception. The evidence base on the effect of contraceptive use among women with mental health disorder would be strengthened by the development of additional studies with strong designs that examine a broader range of hormonal contraceptive methods, have longer follow-up periods, provided a more standardized measure for depression and studied other types of mental health disorders. The information in this review will be incorporated into the forthcoming update of the US Medical Eligibility Criteria for Contraceptive Use.

References

[1]. Kessler RC, Berglund P, Demler O, Jin R, Merikangas KR, Walters EE. Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication. Arch Gen Psychiatry 2005;62:593–602. [PubMed: 15939837]

[2]. Association AP. Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition. Arlington, VA: American Psychiatric Association; 2013.

[3]. Farr SL, Bitsko RH, Hayes DK, Dietz PM. Mental health and access to services among US women of reproductive age. Obstet Gynecol 2010;203:542.e1–9, 10.1016/j.ajog.2010.07.007.

[4]. Hasin DS, Goodwin RD, Stinson FS, Grant BF. Epidemiology of major depressive disorder: results from the National Epidemiologic Survey on Alcoholism and Related Conditions. Arch Gen Psychiatry 2005;62:1097–106. [PubMed: 16203955]

[5]. Phillips ML, Kupfer DJ. Bipolar disorder diagnosis: challenges and future directions. Lancet 2013;381:1663–71. [PubMed: 23663952]

[6]. Tondo L, Lepri B, Cruz N, Baldessarini RJ. Age at onset in 3014 Sardinian bipolar and major depressive disorder patients. Acta Psychiatr Scand 2010;121:446–52, 10.1111/j.600-0447.2009.01523.x [Epub 2009 Dec 23]. [PubMed: 20040069]

[7]. Merikangas KR, Akiskal HS, Angst J, et al. Lifetime and 12-month prevalence of bipolar spectrum disorder in the National Comorbidity Survey replication. Arch Gen Psychiatry 2007;64:543–52. [PubMed: 17485606]

[8]. Magalhaes PV, Kapczinski F, Kauer-Sant'Anna M. Use of contraceptive methods among women treated for bipolar disorder. Arch Womens Ment Health 2009;12:183–5, 10.1007/s00737-009-0060-y [Epub 2009 Mar 10]. [PubMed: 19277844]

[9]. Curtis V Women are not the same as men: specific clinical issues for female patients with bipolar disorder. Bipolar Disord 2005;7:16–24. [PubMed: 15762865]

[10]. Berenson AB, Asem H, Tan A, Wilkinson GS. Continuation rates and complications of intrauterine contraception in women diagnosed with bipolar disorder. Obstet Gynecol 2011;118:1331–6. [PubMed: 22105263]

[11]. Meade CS, Sikkema KJ. Voluntary HIV testing among adults with severe mental illness: frequency and associated factors. AIDS Behav 2005;9:465–73. [PubMed: 16323033]

[12]. Alder J, Fink N, Bitzer J, Hosli I, Holzgreve W. Depression and anxiety during pregnancy: a risk factor for obstetric, fetal and neonatal outcome? A critical review of the literature. J Matern Fetal Neonatal Med 2007;20:189–209. [PubMed: 17437220]

[13]. Stein A, Pearson RM, Goodman SH, et al. Effects of perinatal mental disorders on the fetus and child. Lancet 2014;384:1800–19, 10.016/S0140-6736(14)61277-0 [Epub 2014 Nov 14]. [PubMed: 25455250]

[14]. Yatham LN, Kennedy SH, Parikh SV, et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) collaborative update of CANMAT guidelines for the management of patients with bipolar disorder: update 2013. Bipolar Disord 2013;15:1–4, 10.1111/bdi.12025 [Epub 2012 Dec 12]. [PubMed: 23237061]

[15]. Abajobir AA, Maravilla JC, Alati R, Najman JM. A systematic review and meta-analysis of the association between unintended pregnancy and perinatal depression. J Affect Disord 2016;192:56–63, 10.1016/j.jad.2015.12.008 [Epub Dec 17]. [PubMed: 26707348]

[16]. Hall KS, White KO, Rickert VI, Reame N, Westhoff C. Influence of depressed mood and psychological stress symptoms on perceived oral contraceptive side effects and discontinuation in young minority women. Contraception 2012;86:518–25, 10.1016/j.contraception.2012.04.010 [Epub Jun 4]. [PubMed: 22673038]

[17]. Goldzieher JW, Zamah NM. Oral contraceptive side effects: where's the beef? Contraception 1995;52:327–35. [PubMed: 8749595]

[18]. Westhoff CL, Heartwell S, Edwards S, et al. Oral contraceptive discontinuation: do side effects matter? Obstet Gynecol 2007;196:412.e1–6 [discussion .e6–7].

[19]. Oinonen KA, Mazmanian D. To what extent do oral contraceptives influence mood and affect? J Affect Disord 2002;70:229–40. [PubMed: 12128235]

[20]. Shamseer L, Moher D, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ 2015;349:g7647, 10.1136/bmj.g7647.

[21]. Harris RP, Helfand M, Woolf SH, Lohr KN, Mulrow CD, Teutsch SM, et al. Current methods of the U.S. Preventive Services Task Force: a review of the process. Prev Med 2001;20:21–35.

[22]. O'Connell K, Davis AR, Kerns J. Oral contraceptives: side effects and depression in adolescent girls. Contraception 2007;75:299–304. [PubMed: 17362710]

[23]. Duke JM, Sibbritt DW, Young AF. Is there an association between the use of oral contraception and depressive symptoms in young Australian women? Contraception 2007;75:27–31. [PubMed: 17161120]

[24]. Rasgon N, Bauer M, Glenn T, Elman S, Whybrow PC. Menstrual cycle related mood changes in women with bipolar disorder. Bipolar Disord 2003;5:48–52.

[25]. Koke SC, Brown EB, Miner CM. Safety and efficacy of fluoxetine in patients who receive oral contraceptive therapy. Obstet Gynecol 2002;187:551–5.

[26]. Herzberg BN, Draper KC, Johnson AL, Nicol GC. Oral contraceptives, depression, and libido. Br Med J 1971;3:495–500. [PubMed: 5565516]

[27]. Berry-Bibee EN, Kim MJ, Simmons KB, Tepper NK, Riley HEM, Pagano HP, et al. Drug interactions between hormonal contraceptives and psychotropic drugs: a systematic review. Contraception 2016;94:650–67. [PubMed: 27444984]

[28]. Gavin NI, Gaynes BN, Lohr KN, Meltzer-Brody S, Gartlehner G, Swinson T. Perinatal depression: a systematic review of prevalence and incidence. Obstet Gynecol 2005;106:1071–83. [PubMed: 16260528]

Table 1

Studies of women clinically diagnosed with depressive or bipolar disorders

Author, year, support, country	Study design, population	Contraceptive use	Outcome	Results	Quality, strengths, weaknesses
Koke et al. [25] 2002, Eli Lilly and Company, United States	Prospective cohort analysis of data from 17 RCTs of fluoxetine safety and efficacy 866 women, aged 18–45 years, with diagnosis of major depression 581 treated with fluoxetine (doses ranged from 5 to 80 mg/daily, duration of treatment ranged from 5 to 8 weeks); 79 with OC use and 502 without OC use 256 received placebo; 41 with OC use and 215 without OC use FU: Women had at least 1 post-baseline visit at an unspecified time	OCs at any time during the RCT treatment period Most common types: mestranol/NET (38%), EE/ norgestrel (14%), EE/NET (20%) and EE/LNG (11%); 4.5% used hormone therapy medroxy-progesterone.	Changes from baseline to endpoint in 3 HAMD-17 scores: **1** HAMD-17 total score (50-point scale) **2** Anxiety/ somatization subscale (18-point scale) **3** Retardation subscale (14-point scale)	Approximate reductions from baseline to endpoint scores (values represented graphically vs. numerically in paper): *Fluoxetine (OC* vs. *non-OC*): • Total: −9 vs. −8.75 • Anxiety/somatization: −2.5 vs. −2.5 • Retardation: −3.25 vs. −3 *Placebo (OC* vs. *non-OC):* • Total: −6 vs. −7 • Anxiety/somatization: −1.5 vs. −2 • Retardation: −2 vs. −2.25 Statistical testing not conducted	*Quality:* Level II-2, poor *Strengths*: • Large sample size • Data originated from RCTs *Weaknesses*: • Details of original RCTs not provided • Women not randomized to OC use • OC use self-reported • Misclassification error related to inclusion of medroxyprogesterone users as OC users • Did not examine COCs and POPs separately • Duration and timing of OC use unknown • Did not address confounders • FU duration and endpoint unknown; variable among women • Statistical testing of comparisons of interest not conducted
Rasgon et al. [24], 2003, source of support not stated, United States	Prospective cohort 17 women aged 18–45 years with bipolar disorder enrolled in a ChronoRecord validation study and recruited from a mood disorder clinic and local advertisements; all were taking mood stabilizers, 12 (71%) were taking antidepressants and 6 (35%) were OC users FU: 3 months	OCs (type not specified)	Daily self-reported mood ratings using a 100-mm VAS between the mood extremes of mania and depression; mood entry <40 was considered depression, 40–60 normal and >60 hypomania; for each menstrual cycle, the mean mood for the first 7 days was compared with the mean mood for the last 7 days	• Among OC users, mood in the first 7 days and last 7 days of the menstrual cycle did not significantly change (mean [SD]=50.1 [14.1] vs. 49.1 [12.8], respectively, p=.510). • Among women not using OCs, mood in the	*Quality*: Level II-2, poor *Strengths*: • Self-reported mood rating VAS validated against observer-rated scales • Statistical testing conducted *Weaknesses*: • Small sample size

Author, year, support, country	Study design, population	Contraceptive use	Outcome	Results	Quality, strengths, weaknesses
				first 7 days and last 7 days of the menstrual cycle did significantly change (mean [SD]=38.2 [13.5] vs. 41.3 [12.7], respectively, p=.015).	• Recruitment rate unknown • Comparability of study groups related to baseline characteristics, including mood, unknown • OC use self-reported • OC type unknown • Short FU duration • No discussion of sample size estimation or power analysis • Did not address confounders
Berenson et al. [10], 2011, NICHD, United States	Prospective cohort 841 women with bipolar disorder (I, II or subthreshold) aged 18–44 years from a nationwide health insurance claims database of employed, commercially insured persons; bipolar disorder code present during the year before contraceptive use • DMPA: *n*=182; 31% continueduse • Cu-IUD: *n*=113; 86% continued use • LNGIUD: *n*=139; 87% continued use • Sterilization: *n*=407; 100% continued use FU: 12 months continuous	DMPA, CuT380A IUD, LNG-IUD, sterilization Classified using ICD-9-CM, CPT and HCPCS codes DMPA users received 4 injections within 12-month period	Frequency of hospitalizations for bipolar disorder or depression (since 40% of women diagnosed initially with unipolar depression)	No significant differences were observed in the number of hospitalizations for bipolar disorder or depression among the four contraceptive groups: • Frequency of bipolar disorder hospitalizations for DMPA, LNG-IUD, Cu-IUD and sterilization groups was 11 (6.0%), 5 (3.6%), 6 (5.3%) and 23 (5.7%), respectively. • Frequency of depression hospitalizations for DMPA, LNG-IUD, Cu-IUD and sterilization groups was 4 (2.2%), 1 (0.7%), 1 (0.9%) and 13 (3.2%), respectively.	*Quality*: Level II-2, fair *Strengths*: • Large sample of women with bipolar disorder • High method continuation rates for IUD and sterilization users • Long FU duration • Statistical testing conducted *Weaknesses*: • Poor method continuation rate among DMPA users • Did not adjust for confounders including psychiatric medication use • Generalizability to women without commercial health insurance unknown

CPT, Current Procedure Terminology; Cu, copper; EE, ethinyl estradiol; FU, follow-up; HCPCS, Healthcare Common Procedure Coding System; ICD-9-CM, International Classification of Disease, Ninth revision, Clinical Modification; NET, norethisterone; NICHD, National Institute of Child Health and Human Development; SD, standard deviation; VAS, visual analog scale.

Table 2

Studies of women classified as depressed based on depression scales

Author, year, support, country	Study design, population	Contraceptive use	Outcome	Results	Quality, strengths, weaknesses
Herzberg et al. [26], 1971, source of support not stated, England	Prospective cohort 272 married women, aged 20–45 years, attending a family planning clinic COC group: *n*=218; 37% continued use; 44% stopped or changed COC; 19% lost during FU IUD group: *n*=54; 74% continued use; 13% stopped; 13% lost during FU 75 classified as depressed at baseline None had used COCs or given birth in past year FU: 2, 5, 8 and 11 months	COC: EE 50 mcg+NEA 3 mg, mestranol 75 mcg+lynestrenol 2.5 mg, or mestranol 50 mcg+1 mg NET IUD: type not specified (assumed to be nonhormonal)	Classification of depression based on modified BDI scores (<9) over FU; threshold level selected based on mean scores at baseline; possible total score NR	Among women depressed at baseline: • 58% (11/19) of IUD users were depressed at 2 months vs. 42% (8/19) of continuing COC users and 73% (27/37) of women who stopped/changed COC (ns) • 58% (11/19) of IUD users were depressed at 5 months vs. 24% (5/21) of continuing COC users and 72% (23/34) of women who stopped/changed COC (p<.01) • 42% (8/19) of IUD users were depressed at 8 months vs. 11% (2/18) of continuing COC users and 56% (18/32) of women who stopped/changed COC (p<.01) • 40% (6/15) of IUD users were depressed at 11 months vs. 16% (3/19) of continuing COC users and 59% (16/27) of women who stopped/changed COC (p<.05)	*Quality:* Level II-2, poor *Strengths*: • Study groups comparable related to age and social class • Statistical testing conducted • Moderate FU rate overall (82%) with little variation by group *Weaknesses*: • Sample selection uncertain and recruitment rate unknown • No discussion of sample size estimation or power analysis • Small sample of women classified as depressed at baseline • OC use self-reported • Poor method continuation rate overall (44%) with substantial variation by group • Short FU duration • Did not address confounders • Depression medication use unknown
Duke et al. [23], 2007, Australian Government's Department of Health and Aging, Australia	Prospective cohort 9688 women aged 18–23 years who completed Survey 2 (2000); women surveyed again in 2003 (Survey 3); initially randomly selected from a national health insurance database in 1996 68% and 64% of women from Survey 1 responded to Survey 2 and Survey 3, respectively	OCs (type not specified), current use	Classification of depression based on CESD-10 score (30-point scale) at Survey 3; women classified as depressed if CESD-10 score ≥10	Among women depressed at Survey 2: • Women who started using OCs between Surveys 2 and 3 had increased odds of no longer being depressed by Survey 3 than women not using OCs on both Surveys 2 and 3 (OR=1.43, CI=1.04–1.96); after adjustment, results no longer significant (OR=1.15, CI=0.75—1.76). • Women who used OCs on both Surveys 2 and 3 had increased odds of no longer being depressed by Survey 3 than women not using OCs on both Surveys 2 and 3 (OR=1.33,	*Quality:* Level II-2, fair *Strengths*: • Moderate response rates • Large sample of women classified as depressed at Survey 2 • Statistical testing conducted • Adjusted for potential confounders

Author, year, support, country	Study design, population	Contraceptive use	Outcome	Results	Quality, strengths, weaknesses
	2488 classified as depressed at Survey 2 FU: 3 years			CI=1.05–1.70); after adjustment, results no longer significant(OR=1.01,CI=0.73–1.41)	• Long FU *Weaknesses:* • Response rate for baseline survey low (41%) • OC use self-reported • OC type unknown • Duration of OC use unknown • Timing of OC use relative to outcome assessment unknown • Depression medication use unknown • Confounders adjusted for in modeling unknown
O'Connell et al. [22], 2007, NICHD, United States	RCT 76 urban adolescent girls aged ≤19 years experiencing dysmenorrhea from an academic medical center; mean CES-D score was 16.8 COC group: *n*=38; 89% continued use; 0% lost during FU Placebo group: *n*=38; 92% continued use; 3% lost during FU 11 classified as depressed at baseline None had recently used HC or ever given birth FU: 3 months	COC (EE 20 mcg/LNG 100 mg	Change in CESD score (60-point scale) over FU Adolescents classified as depressed if CESD score≥27; threshold level selected based on 1 SD above the mean score at baseline (Note: scores of ≥16 commonly interpreted as indicative of depression)	Among adolescents depressed at baseline overall, CESD scores significantly (p=.003) decreased from baseline (mean=35.7, SD=8.5 to endpoint (mean=19.1, SD=9.2), with similar improvements in the COC and placebo groups (data not reported).	*Quality:* Level II-2, poor *Strengths:* • Study groups comparable related to baseline characteristics • High treatment continuation rate overall (91%) with little variation by group • Minimal loss during FU *Weaknesses*: • Randomization procedures unknown • Low (44%) participation rate among eligible adolescents • Small sample of women classified as depressed at baseline • OC use self-reported • Differences in CES-D reductions among OC and placebo groups not statistically examined • Depression medication use unknown

Author, year, support, country	Study design, population	Contraceptive use	Outcome	Results	Quality, strengths, weaknesses
					• Short FU duration

BDI, Beck Depression Inventory; EE, ethinyl estradiol; FU, follow-up; NEA, norethisterone acetate; NET, norethisterone; NICHD, National Institute of Child Health and Human Development; NR, not reported; NS, not significant; SD, standard deviation.